D40589ELP

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)


(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 November 2001 (22.11.2001)

PCT

(10) International Publication Number
WO 01/87385 A1

(51) International Patent Classification[7]: A61M 5/30, 5/178

(21) International Application Number: PCT/GB01/02156

(22) International Filing Date: 16 May 2001 (16.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0011615.2 16 May 2000 (16.05.2000) GB
0027402.2 9 November 2000 (09.11.2000) GB



(71) Applicant (*for all designated States except US*): WESTON MEDICAL LIMITED [GB/GB]; 2a Hales Barn Workshops, New Street, Stradbroke, Eye, Suffolk IP21 5JG (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): WESTON, Terence, Edward [GB/GB]; Thornlea, Pixey Green, Stradbroke, Eye, Suffolk IP21 5NG (GB). NUSSEY, Matthew, Simon [GB/GB]; 723 Worrall Road, Worrall, Sheffield S35 0AU (GB).

(74) Agent: ELKINGTON AND FIFE; Prospect House, 8 Pembroke Road, Sevenoaks, Kent TN13 1XR (GB).



(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.


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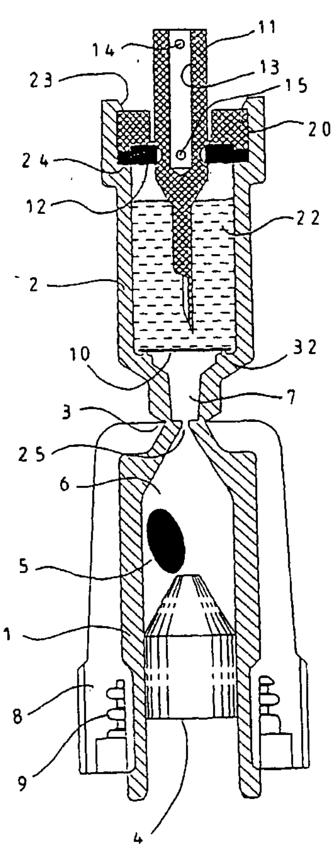
(54) Title: LIQUID TRANSFER DEVICE FOR DRUG RECONSTITUTION OR LIQUID DRUG TRANSFER





(57) Abstract: A device and method for reconstituting a lyophilised drug, wherein the drug is stored under vacuum in one compartment of the device, and the solvent in another compartment at substantially atmospheric pressure, and means for connecting the compartments so that the vacuum causes solvent to flow into the drug compartment, thereby dissolving the drug. Alternatively, the drug or other material may be stored in liquid form in one compartment of the device, and caused to flow into another by the use of a vacuum.


WO 01/87385 A1

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# Liquid transfer device for drug reconstitution or liquid drug transfer

## BACKGROUND TO THE INVENTION

A number of drugs are not stable in aqueous solution, and must be stored in a dried form. When first manufactured, such drugs are aqueous, and the dried form is attained by a process known as freeze drying or lyophilisation, whereby the drug is subjected to a vacuum to extract the water. Some drugs may not be aqueous, and a solvent other than water might be used. Where reference is made below to water as a solvent it is to be understood that another solvent might be used instead.

Most of the lyophilised drugs are for parenteral administration by hypodermic syringe or needleless injector, and it is necessary to reconstitute the drug before use by adding a quantity of water equivalent to that which was removed from the original solution, or some other amount to render the drug suitable for absorption. A common method is to present the dried drug in a sealed vial having a pierceable membrane closure, and to introduce the required quantity of water with a hypodermic needle through the closure. Good practice requires that a second hypodermic syringe is used to withdraw the required quantity of reconstituted drug, and used to administer the dose to the patient. This method, although widely used, is time consuming and also wasteful, because it is always necessary to make up rather more drug than required for the injection, and since the aqueous drug is unstable, the excess must be discarded.

Other methods utilise devices based on a hypodermic syringe having two compartments, wherein the drug is stored in one, water in the other, and by moving the syringe plunger, the water is pressurised and caused to flow from a second compartment into the drug compartment. The connection between the two compartments is made by either rupturing a separating membrane, or by valve means to cause a channel to connect the compartments. Such devices are more or less automatic, in that the correct quantity of water is transferred with one relatively simple operation. There is a drawback however, because the user is required to complete the stroke of the syringe plunger to transfer the correct amount of water, and therefore it is possible to have insufficient water to completely dissolve the drug.

Needleless injectors are being used increasingly as an alternative to conventional hypodermic syringes, and use a powerful jet of liquid drug to first

penetrate the epidermis and then deposit in the underlying tissues. When used for reconstituted drugs, the construction of these devices usually requires that the drug compartment is filled immediately before use, and there are various injectors that use a drug transfer device between a vial and the drug compartment. These methods are suitable for drugs which have been reconstituted in a vial, but are just as time consuming and wasteful as the basic method used for hypodermic syringe filling. All of the prior art methods require a high degree of expertise and training, which limits the use of lyophilised drugs to healthcare professionals and those patients who need to self-administer such drugs on a regular basis and are familiar with the procedures.

One aspect of the invention aims to provide a convenient prefilled needleless injectors which has means for reconstituting a lyophilised drug within the device.

Another aspect of the invention relates to drugs in liquid form which require to be stored in a container constructed from a drug-compatible material That material may not be strong enough to withstand the stresses produced during needleless injector (often as high as 600 bars), and this other aspect of the invention aims to address this problem.

## DESCRIPTION OF THE INVENTION

The present invention provides a method and apparatus for reconstituting lyophilised drugs in a needleless injector drug capsule (or variously called cartridge, chamber, ampoule, carpule, etc.) which is both more accurate and easier to use than those found in the prior art. Alternatively, the drug may be in liquid form and be transferred by vacuum from a storage compartment to a dispensing compartment. In both applications, the constructions are very similar.

Lyophilised drugs are extremely hygroscopic, and need to be stored in a sealed dry atmosphere or in a vacuum. The present device comprises an evacuated chamber containing the freeze dried drug, separated from a second chamber containing the water. Means is provided for connecting the chambers so that atmospheric pressure causes the water or other solvent to flow into the drug chamber. The evacuated chamber is of a predetermined volume, so that the correct amount of water is automatically transferred.

In a first preferred embodiment, the two chambers are separated by a membrane, and a piercing member is provided which causes the atmospheric pressure to force the water into the drug chamber. The initial part of movement by the piercing member opens a vent to atmosphere in the water chamber, so that the full atmospheric pressure is available to effect the transfer, and the remainder of the movement pierces the membrane to connect the chambers. The chamber which contained the water is then detached, exposing the delivery orifice of the drug chamber.

In a second preferred embodiment, two chambers are provided, one containing the dried drug, the other the water. A connecting conduit is sealed with a removable resilient plug, and the drug chamber is evacuate. The resilient plug is connected to a sealing closure in the water chamber, and when the closure is removed, the first part of the movement opens a port in the water chamber to the atmosphere, and completion of the movement removes the resilient plug from the connecting conduit. The water is thus transferred to the drug chamber under the action of atmospheric pressure. The chamber which contained the water is then detached, exposing the delivery orifice of the drug chamber.

In a third preferred embodiment, the solvent is contained within a collapsible tube. Means are provided to connect the outlet of the collapsible tube to the evacuated drug dispensing chamber, so that the air pressure acting on the tube causes the solvent to flow from the tube and into the drug dispensing chamber.

A fourth preferred embodiment is similar to the third, except that the drug is stored in the collapsible tube in liquid form, and then transferred to the empty evacuated dispensing chamber.

A common feature of the first two preferred embodiments is that the water chamber is first opened to the atmosphere before the connecting means is enabled. This maximises the pressure difference between the chambers and ensures efficient transfer. In the collapsible tube embodiment, it is not necessary to open the solvent to atmosphere. Another common feature of all embodiments is that there is preferably provided a slight excess of water in the water chamber, to guarantee complete filling of the evacuated drug chamber. Any excess water is contained within a reservoir in the detachable water chamber and discarded. Preferably the detachable water chamber is "tamper evident", that is, it provides unambiguous evidence that the

device has been operated, and furthermore, that it cannot be re-assembled. The preferred embodiments use a frangible connection between the chambers.

In summary, the invention provides, in various embodiments, a device in which a solvent, or drug, or other substance, in liquid form, is initially held in a first chamber, and is transferred prior to use by atmospheric pressure into a second chamber in which a vacuum has previously been maintained, the second chamber either containing a drug for reconstitution by the solvent, or providing a space to receive the drug, or other substance, in liquid form.

By way of prior art attention is directed to US-A-4010747, which purports to describe a method of filling a needleless injector ampule by initially evacuating the ampule and thereafter connecting it to a vial containing a medicament. However, the method described there is believed to be completely impractical, since either the vial must be completely full of liquid prior to connecting it to the ampule, in which case no liquid will transfer, or it must contain air or other gas, in which case bubbles will enter the ampule along with a volume of liquid which cannot be predetermined. The present invention overcomes these problems and enables a precise dose of substantially bubble-free liquid to be transferred.

A detailed description of the preferred embodiments, with reference to the drawings, is set out below. It should be noted that the drawings generally refer to a device having a circular cross section, but that other cross sections may be adapted to fulfil the objective of the invention. Whilst only the drug capsule is shown and described, it may be pre-assembled to an actuator (i.e., the power unit and firing mechanism), or form an integral part of an injector, or be assembled by the operator to an actuator after reconstituting the drug. One suitable actuator is described in WO 96/28202 and, with a modification, in WO 97/37705.

Figure 1A is a longitudinal cross-section through a cylindrical needleless injector drug capsule according to the first embodiment, comprised of an inner drug contact part with an outer layer of protective plastic, and a membrane separating the drug container and the water chamber. A piercing tube is shown in Figures 1B and 1C, and Figure 1D shows the principle of operation of the piercing tube.

Figures 2A to 2D show the sequence for preparing the drug capsule.

Figures 3A to 3D show the sequence for preparing the drug capsule according to the second embodiment, which employs a resilient plug to separate the compartments.

Figure 4A shows an embodiment containing a liquid drug prior to freeze drying, and having a collapsible tube containing a solvent for reconstituting the drug after freeze drying.

Figures 4B to 4E show the stages required for reconstituting the drug and preparing the drug capsule for use.

Figures 5A to 5E are similar to Figures 4D to 4E, except that there is no freeze dried drug, the liquid drug being stored in the collapsible tube prior to vacuum transfer to the dispensing chamber.

Referring to Figure 1A, drug chamber 1 is connected to the water chamber 2 by the frangible connection 3. A sleeve 8 surrounds the drug chamber 8, and has a screw thread 9 by which the drug capsule may be connected to the operating device. The reason for this construction is that the drug contact material may be glass or a plastic material which requires the protection and support of a sleeve, but of course it is possible to make the entire component from one material only if the application permits.

Chambers 1 and 2 are separated by the membrane 10, which is sealingly attached to a mounting surface 32, and the piston 4 seals the volume 6. The piston 4 is positioned so that the volume 6 between the piston 4 and injection orifice 25 is that required for the volume of reconstituted drug. The drug chamber 1 contains the lyophilised drug 5, and the volume 6 is held under a vacuum. The friction between the piston 4 and the bore of chamber 1 is sufficient to prevent movement of the piston 4 as a result of the pressure exerted by the atmosphere, and the membrane 10 is sufficiently strong to resist damage by the pressure difference. Furthermore, the membrane 10 should be able to withstand prolonged contact with water. The piston 4 and membrane 10 should have good sealing properties to prevent undue loss of vacuum. The total evacuated thus comprises the volume 6 within the chamber 1, and a small reservoir 7 in chamber 2, the two being in hydraulic communication via the injection orifice 25.

The open end of chamber 2 carries a piercing tube 11. As shown in Figure 1B, the piercing tube 11 has a bore 13 in one end, through which an air inlet hole 14 and outlet hole 15 are located. Hole 15 is located also on the centreline of a curved section groove 16. The other end of the piercing tube 11 is the cutter 17. Figure 1C is an enlarged view of the cutter 17, showing the section shaped in the form of a crescent, 18, and tapered to a sharp tip 19. The piercing tube 11 is frangibly attached at 21 to a carrier 20.

Referring to Figure 1A, the piercing tube 11 is assembled to a resilient seal 12 having a central aperture therein. The seal 12 is in the form of a washer, and preferably made from a pharmaceutical grade rubber. The edges of the aperture in the seal must be sharp and free from surface defects, so that when the edges are in contact with the curved surface of groove 16 it forms a seal against the ingress of bacteria. (This type of seal is commonly used to seal the stem of aerosol valves used for dispensing cosmetics, paint, and many other products, and in that context, will efficiently seal against loss of pressurised propellant gas for many years). The water chamber is filled with water 22, and the sub-assembly of piercing tube 11 and its carrier 20, plus seal 12, is assembled into the water chamber 2 and retained by lugs 23. A slight compression is applied by the lugs 23 to the carrier 20, so that the seal 12 is sealingly pressed against the abutment 24.

Referring now to Figure 2A, this shows the assembled and filled drug capsule, as previously described, and Figure 2B shows the initial effect of pushing in the stem of the piercing tube 11 in the direction of arrow X. The frangible connection 21 is broken, and the seal 12 is deflected, so that the lower edge of the hole in the seal 12 breaks away from the curved face of groove 16 of the piercing tube 11. This connects the inside of the water chamber 2 to atmosphere via hole 15, bore 13 and hole 14. (Hole 14 provides an air entry hole if the end of bore 13 is blocked by the user, but a groove in the end face of piercing tube 11 would suffice, and hole 14 then becomes unnecessary). This is shown in more detail in the enlarged view of the water chamber in figure 1D

Further movement of the piercing tube 11, as shown in Figure 2C, causes the sharp tip 19 of the cutter 17 to pierce the membrane 10. The crescent shape 18 (Fig.1C) of the cutter causes a flap type of perforation in the membrane 10. The two

chambers, 1 and 2, are now in communication via the reservoir 7 and orifice 25. The vacuum in chamber 1 therefore deflects the flap and draws in the water 22 from chamber 2 until it fills chamber 1, and dissolves the drug 5. Because the vacuum will not be absolute, the reservoir 7, being also evacuate with chamber 1, provides excess vacuum to that required to fill the chamber 1, and a small amount of excess water remains in the reservoir 7. The piston 4 will have been already correctly positioned within the bore of chamber 1, so that the exact volume of water is transferred. During the transfer of water, air is drawn in through the bore 13 of the piercing tube 11 and hole 15, so that the full difference between the vacuum and atmospheric pressure is used to cause the transfer of water 22.

The filling takes a second or so, and afterwards, the water chamber 2, complete with piercing tube 11, seal 12, membrane 10 and the excess water, is snapped of at frangible connection 3 and discarded, as shown in Figure 2D. The capsule may then be attached to an actuator, (or it may have been pre-assembled to an actuator), and the injection may then be administered.

Referring now to Figures 3A to 3D, the assembly is similar to the "pierced membrane" embodiment described, except that the membrane and piercing tube are replaced by a resilient plug and sealing cap connected thereto. Figure 3A shows the assembled drug capsule comprising a drug chamber 1, connected to the water chamber 2 by the frangible connection 3. A sleeve 8 surrounds the drug chamber 8, and has a screw thread 9 by which the drug capsule may be connected to the operating device. The reason for this construction is that the drug contact material may be glass or a plastic material which requires the protection and support of a sleeve, but of course it is possible to make the entire component from one material only if the application permits. The piston 4 seals the volume 6, and is positioned so that the volume 6 between the piston 4 and injection orifice 25 is that required for the volume of reconstituted drug. A small reservoir 7 is located at one end of the water chamber 2 and connects to the drug chamber 1 via the injection orifice 25. A resilient plug 26 is sealingly inserted into the reservoir 7. The drug chamber 1 contains the lyophilised drug 5, and the volume 6 is held under a vacuum. The friction between the piston 4 and the bore of chamber 1 is sufficient to prevent movement of the piston 4 as a result of the pressure exerted by the atmosphere. The resilient plug 26 is able to maintain a vacuum-tight seal and resist deterioration by the water for reconstitution.

The water chamber 2 is filled with the required volume of water 22, and a cap 28, which has a longitudinally extending barb 29 and a sealing ring 27, is inserted into the open end of the chamber 2. The barb engages with a hole in the resilient plug 26 so that the resilient plug 26 becomes firmly attached to the cap 28. Seal 27 prevents bacterial contamination of the water 22.

Figure 3B shows the first stage of preparation, whereby the cap 28 is pulled out a small distance in the direction of the arrow X. This drags the resilient plug 26 partly out of the reservoir 7; note that the plug 26 still seals in against the wall of reservoir 7 to prevent loss of the vacuum in the drug chamber 1. A slot (or hole) 30 through the wall of water chamber 2 is uncovered by the seal 27, and connects the water chamber to atmospheric air. As shown in Figure 3C, further withdrawal of the cap 28 removes the resilient plug 26 completely from the reservoir 7, which brings the drug chamber 1 and water chamber 2 into hydraulic connection via the injection orifice 25, and the vacuum within the drug chamber 1 draws in the water 22 from water chamber 2. There is an excess of water 22 available, which remains in the reservoir 7. The filling takes a second or so, and afterwards, the water chamber 2, complete with cap 28, seal 27, plug 26, and the excess water, is snapped of at frangible connection 3 and discarded (Fig.3D). The capsule may then be attached to an actuator, (or it may have been pre-assembled to an actuator), and the injection may then be administered. Although not shown, the cap 28 may be frangibly attached to the water chamber to provide tamper evidence.

Figure 4A illustrates the third preferred embodiment and shows a drug capsule 101 which may have one or more layers 101, and which has been filled with the required volume of drug 115 in liquid form. This volume is the space between a piston 104 and an injection orifice 112. The drug capsule 101 has screw threads or other means 116 for attaching the capsule to a power source for dispensing the drug. 16 Piston 104 is able to sealingly slide within the bore of the drug capsule 101 but has sufficient friction to resist movement when the pressure difference across the piston is slightly more than one atmosphere. The drug capsule 101 has a connector 102 attached, preferably frangibly so, at 103, and connector 102 carries at least one resilient sealing element 105. A reservoir 106 for water or other solvent is assembled over the connector 102, but without sealing on the seals 105. The reservoir 106 has a tube 107 sealing attached and closed by a pierceable membrane 110 and crimped seal

107. The tube 107 contains the water, or other solvent, 108 for reconstitution, preferably de-gassed and without entrapped bubbles of gas. Pierceable membrane 110 may be integral with the tube 107, or with the reservoir 106, the objective being to seal the contents from the atmosphere. Any two, or all three, of the tube 107, reservoir 106 and membrane 110 may, if desired form a single integrally formed unit. The tube 107 may, if desired, be lined with a material to enhance its storage properties. Between the injection orifice 12 and the membrane 110 there is a conduit 113 which is in gaseous connection with a cavity 114. A membrane cutter 111 is attached to, or integral with, the end face of the connector 102.

Part of the freeze drying process requires a vacuum to be applied to the drug to be dried. This is done in this embodiment by placing the whole device in a vacuum chamber, and drawing air through the gap between the connector 102 and slots 118 in the reservoir 106, as indicated by arrow E. When the freeze drying process is completed, and with the assembly still subjected to a vacuum, the reservoir 106 is pushed further onto the connector 102 in the direction of arrow X, so that the seals 105 seal on the bore of cavity114. Thus the freeze dried drug, diagrammatically indicated at 119 in Figure 4B, is contained within the evacuated capsule void 120, which is in communication with the conduit 113 and cavity 114.

When it is required to reconstitute the drug 119, the reservoir 106 is pushed in the direction of arrow X, so that the cutter 111 pierces the membrane 110 to make a flap therein through which the water 103 may flow, as shown in Figure 4C. Atmospheric pressure acting on the collapsible tube 107 squeezes the tube 107 to force the water 108 through the ruptured membrane 110, the conduit 113, the injection orifice 112 and into the drug capsule void 120. The water dissolves the freeze dried drug 119, and since the void 120 is the volume which was previously occupied by the liquid drug 115 (Fig.4 A) the amount and concentration of the reconstituted drug is the same as the original.

It is to be noted that the reservoir 106 is pushed onto the drug capsule 101 in the manner described above, dogs 117 on the connector 102 engage with slots 118 on the reservoir 106. The final steps in the preparation of the capsule are to twist the reservoir 106 relative to the capsule 101, and because the reservoir 106 is engaged with the connector 102 via the dogs 117 and slots 118, it shears from the capsule 101

at the frangible connection 103. It will be seen that this shearing operation cannot be carried out before the reservoir 106 is pushed on to the capsule 101, and this cannot be carried out before reconstitution has taken place. The reservoir 106 and connector 102 are discarded and the capsule is ready to give an injection.

In the fourth embodiment, shown in Figure 5A, the components are the same as those described in the third embodiment (Figures 4A to 4E ) except that the drug is stable in its liquid form and stored within the collapsible tube. Thus there is no freeze drying cycle, although the void 120 is still evacuated to provide the necessary pressure difference to allow the atmospheric pressure to squeeze the collapsible tube.

In a further embodiment (not illustrated), the liquid in the liquid chamber may be separated for atmosphere by a piston whose upper end is exposed to atmosphere from the outset, or at least immediately prior to use. The liquid is thus under atmospheric pressure as a result of the piston bearing on it. This pressure is effective to transfer the liquid to the drug capsule. In the case of a piston which is only exposed to atmosphere immediately prior to use, the transfer can take place immediately this exposure occurs. In the case of a piston which is exposed to atmosphere from the outset there needs to be some mechanism to prevent transfer until the desired amount. If atmospheric pressure also is not sufficient, the piston may be subjected to a spring force which supplements the atmospheric pressure.

In all of the embodiments described, it is not necessary for the user to pause during pushing in the piercing tube or extracting the resilient plug, as the case may be, and accurate reconstitution or drug transfer may be accomplished with one simple operation.

It may be required to be able to maintain a vacuum in the drug chamber for many years, so that where the drug is lyophilised the drug is maintained in the dried condition, and to ensure that there is sufficient vacuum to draw in the required volume of water or drug. If this is required it may be desirable to place the filled drug capsule into a further pouch or pack, which is then evacuated. This will minimise the pressure difference across the piston and reduce the likelihood of reduced vacuum due to a slow leakage of air into the drug chamber.

## CLAIMS:

1. A liquid transfer device comprising a first element defining a first chamber having a liquid therein, a second element defining a second chamber at sub-atmospheric pressure, and a structure for communicating the first chamber with the second chamber to enable liquid to pass from the first chamber to the second chamber while liquid in the first chamber is subjected to atmospheric pressure.

2. A device according to claim 1, wherein the second chamber contains a drug in lyophilised form, and the liquid in the first chamber is a solvent for the said drug.

3. A device according to claim 1, wherein the liquid in the first chamber is a drug in liquid form.

4. A device according to any preceding claim, wherein the second element is in the form of a needleless injector capsule having an injection orifice and a piston, the second chamber being located between the injection orifice and the piston.

5. A device according to claim 4, wherein the second element is connected to the first element via a portion thereof defining the injector orifice, whereby passage of liquid from the first chamber to the second chamber is through the injection orifice.

6. A device according to claim 5, wherein the second element is connected to the first element by a frangible connection.

7. A device according to any preceding claim, wherein the said structure is adapted successively to:

(i) communicate the first chamber with atmosphere; and

(ii) communicate the first chamber with the second chamber.

8. A device according to claim 7, wherein the said structure comprises an actuator member movable from a first rest position to a second position in which it allows atmospheric pressure to enter the first chamber and thence to a third position in which the first chamber communicates with the second chamber.

9. A device according to claim 8, in which the said actuator member is an elongate member having an upper tubular portion having an air inlet and an air outlet, the air inlet being in communication with atmosphere, and the air outlet being sealed from the first chamber when the actuation member is in its first position and being in communication with the first chamber when the actuation member is in its second and third positions.

10. A device according to claim 8 or 9, wherein the first element has a membrane preventing the liquid in the first chamber from entering the second chamber, and the actuation member carries a perforating means operable, as the actuation member moves from its second to its third position, to perforate the membrane.

11. A device according to claim 8, wherein the actuation member comprises a plug which, in the rest position of the actuation member prevents liquid in the first chamber from entering the second chamber, the plug being movable to allow the first chamber to communicate with the second chamber as the actuator member moves from its second position to its third position.

12. A device according to any one of claims 1 to 6, wherein the first chamber has a volume which varies with the volume of liquid therein and transmits atmospheric pressure to the liquid therein.

13. A device according to claim 12, wherein the first chamber is defined by a flexible member.

14. A device according to claim 12 or 13, wherein the first and second elements are capable of movement in a direction towards one another, and the said structure for communicating the first chamber with the second chamber comprises a means for perforating the first chamber during the said movement.

15. A device according to claim 14, wherein the second element is connected to the first element by a frangible connection, and wherein the said movement causes interengagement between members on the first element and members on the second element such that a rotational force applied to one element relative to the other after interengagement causes the frangible connection to break.

16. A device according to any preceding claim, wherein the volume of liquid in the first chamber is greater than the volume of the second chamber, whereby after liquid has passed from the first chamber to the second chamber, a residual volume of liquid remains outside the second chamber but in fluid communication with the liquid in the second chamber.

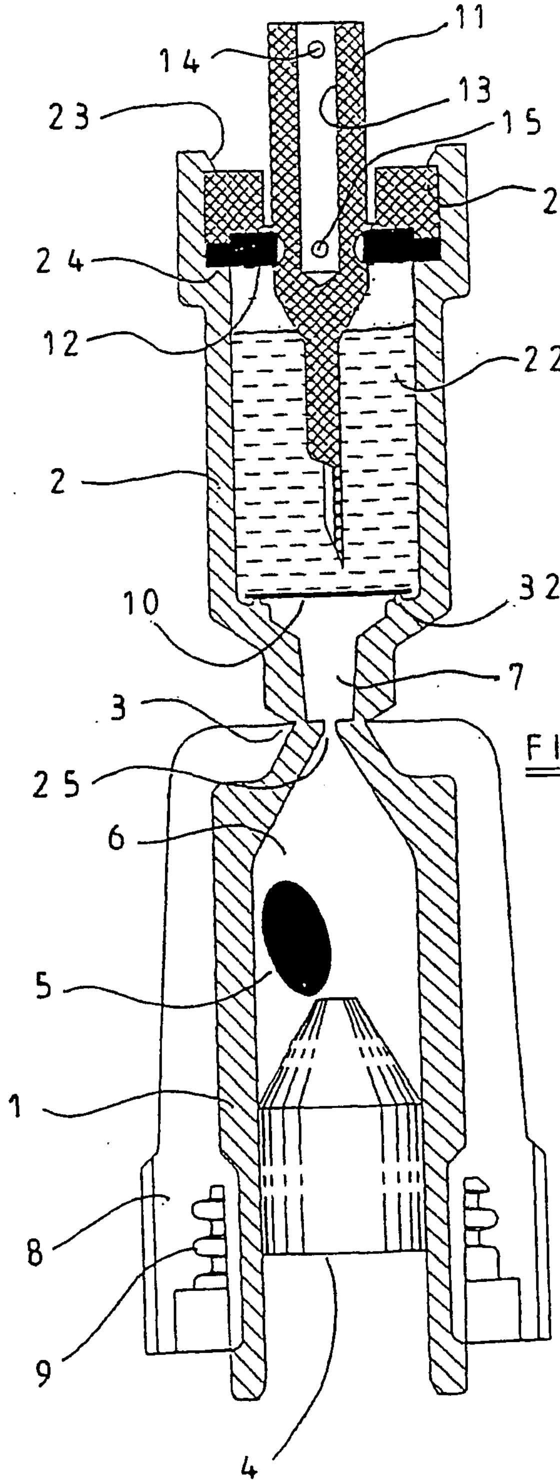
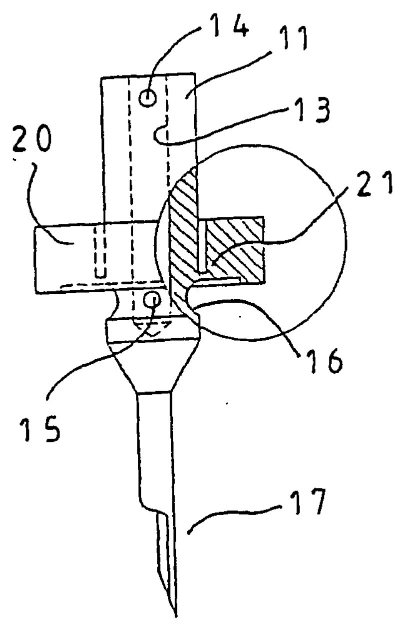



FIG 1A

FIG 1B



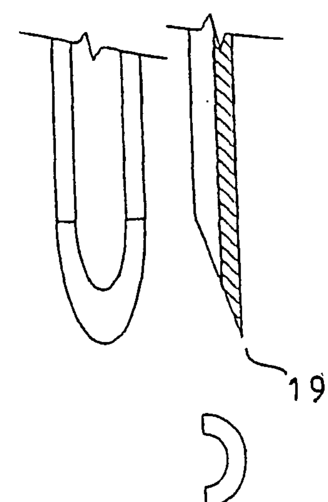




FIG 1C

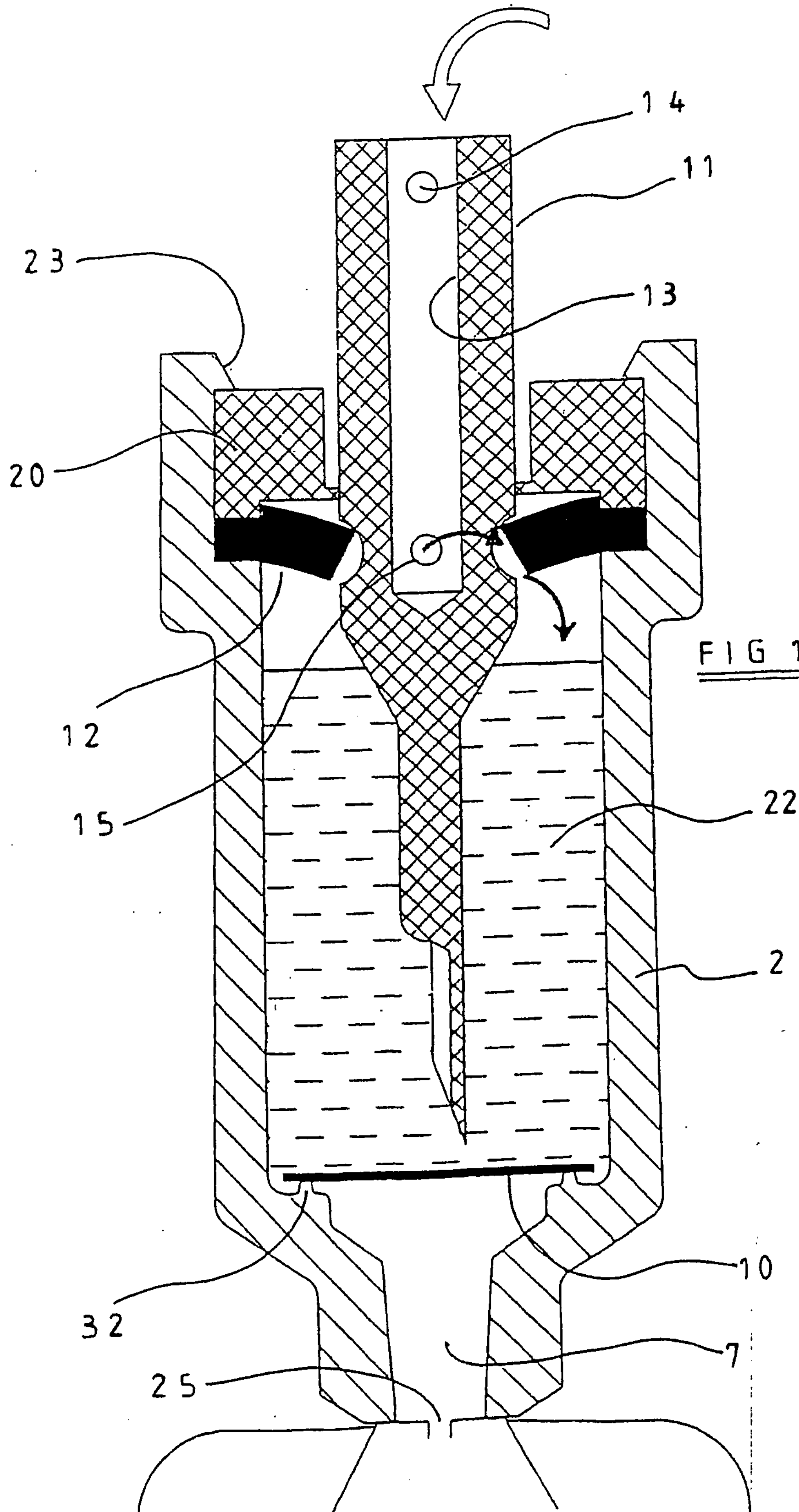



FIG 1D

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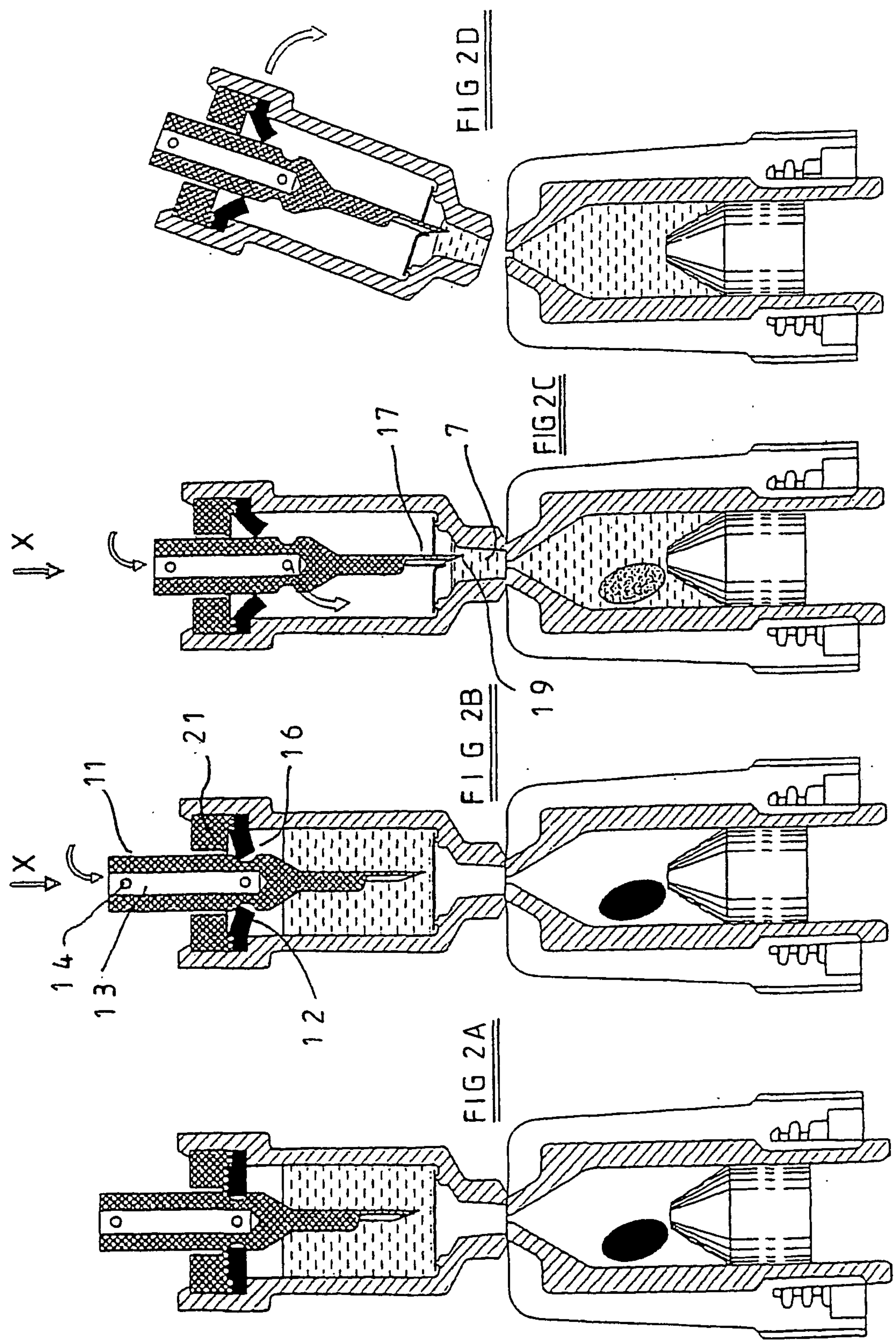
FIG 2D
FIG 2C
17
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X
19
FIG 2B
21
16
11
X
14
13
12
FIG 2A

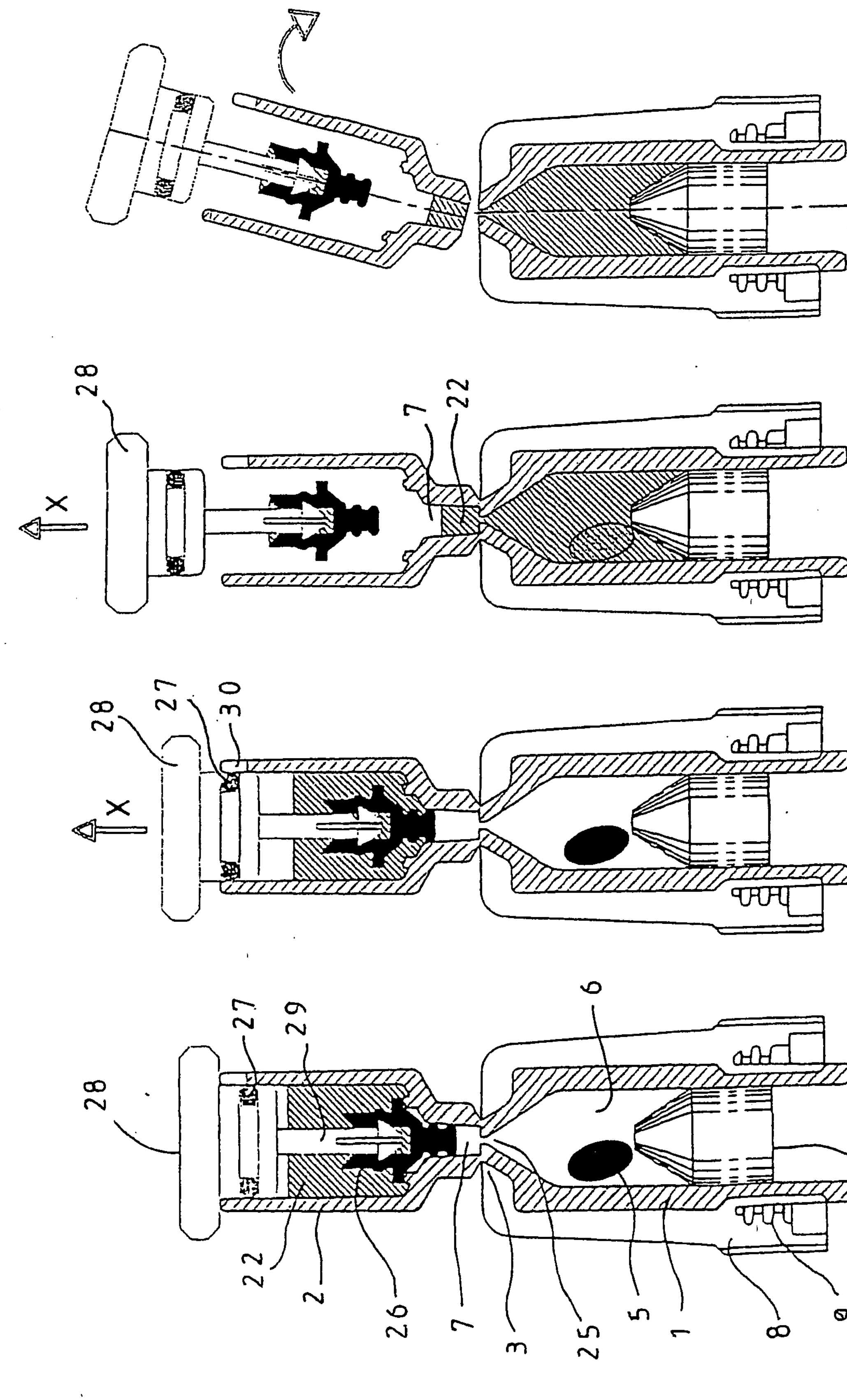


FIG 3A

FIG 3B

FIG 3C

FIG 3D

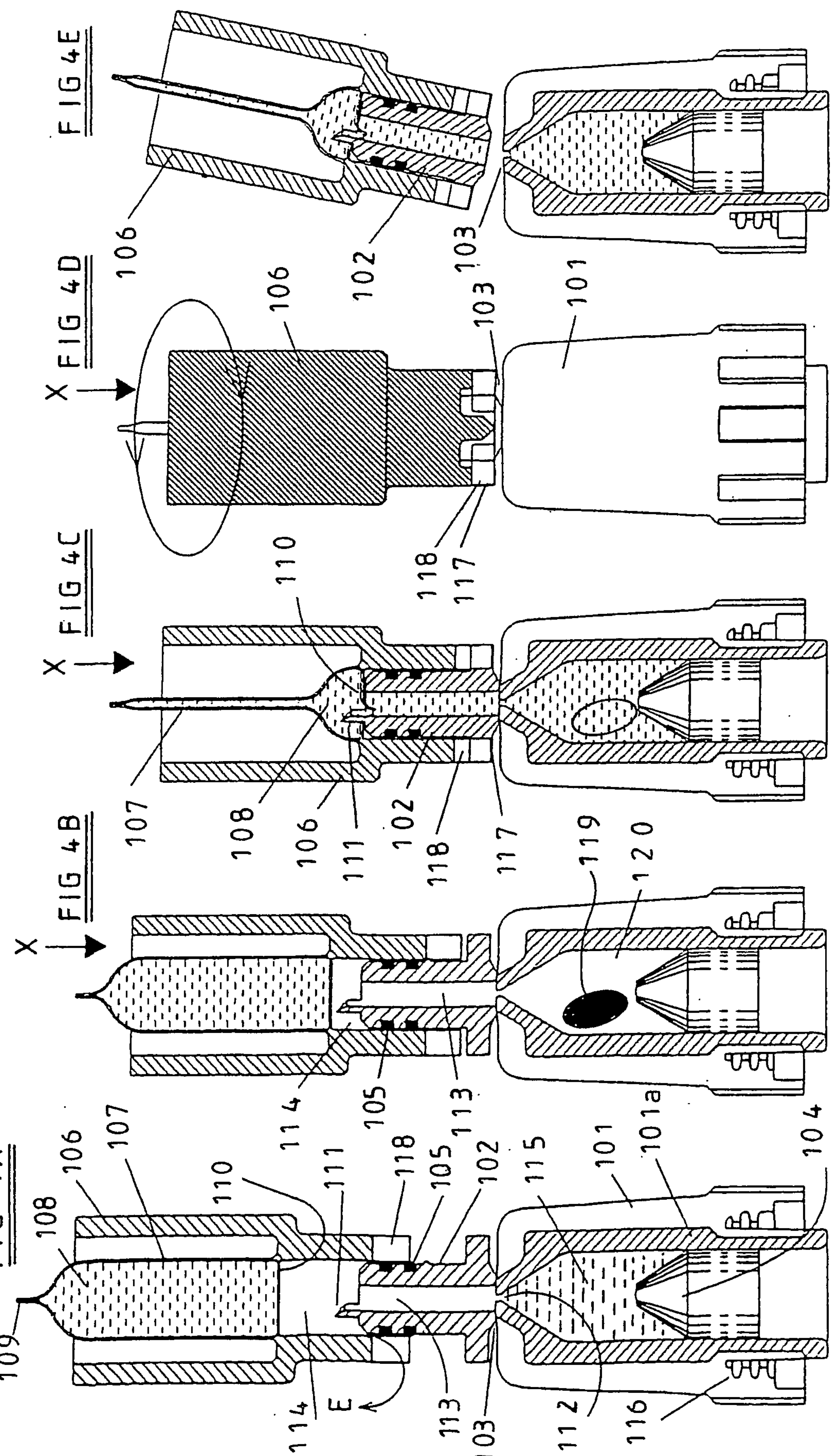


FIG 4A
FIG 4B
FIG 4C
FIG 4D
FIG 4E

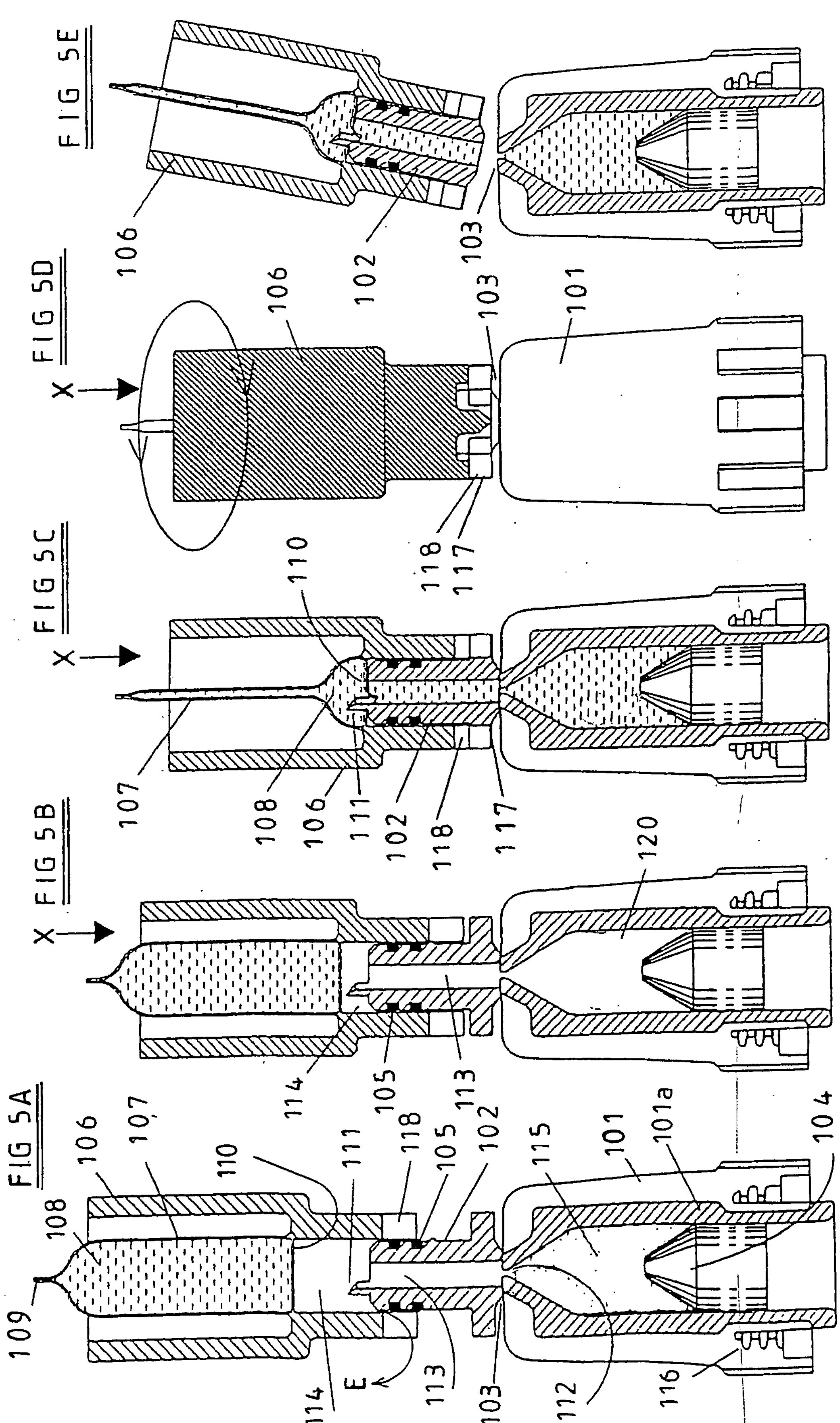
FIG 5A
FIG 5B
FIG 5C
FIG 5D
FIG 5E
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# INTERNATIONAL SEARCH REPORT

Inter[illegible]ial Application No
PCT/GB 01/02156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/30 A61M5/178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 August 2001 | 20/08/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Sedy, R |

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